MicroRNAs: small molecule, big potential for coronary artery disease

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This editorial refers to 'Transcoronary gradients of vascular miRNAs and coronary atherosclerotic plaque characteristics', by D.M. Leistner et al., on page 1738.

MicroRNAs (miRs), the diminutive epigenetic silencing phenomena only recently discovered, are moving tantalizing close to becoming a realizable diagnostic and therapeutic focus for coronary artery disease (CAD), and the results presented in this issue of the journal just may have provided supportive data allowing that work to begin in earnest intent on achieving that goal. These small non-coding nucleotide sequences that repress protein translation by binding to competing sequences have been shown to be contributory to pathologies from renal and neural diseases to obesity and alcoholism. In their manuscript, Leistner et al. present a noteworthy contribution to a potential link between tenuous coronary pathology and miRs. Notably, the authors describe associations between the overall plaque burden in addition to gradients from the arterial to venous aspects of the coronary circulation with respect to miR-126-3p, miR-145-5p, miR-155-5p, and miR-29b-3p. Furthermore, the authors also demonstrate the predictive power of these transcoronary gradients of miR-126-3p, miR-126-5p, miR-145-5p, miR-15-5p, and miR-29b-3p in detecting potentially vulnerable plaques as indicated by thin-cap fibroatheromas (TCFAs) by integrating optical coherence tomography (OCT), a novel intracoronary imaging modality. Although the data are cross-sectional in nature, and the usual miR methodological concerns should be heeded, these authors have provided hypothesis-generating data for a potential link between the pathophysiology of vulnerable plaques and miRs.

Importantly, the authors use a physiological approach by gathering transcoronary gradients of the miRs in patients appropriately undergoing coronary angiography coupled with the anatomic advantages offered by OCT to image atherosclerotic plaques. The resultant data are able to couple either production or consumption within the coronary circulation of miRs deemed relevant for CAD with TCFAs in the left coronary artery tree. While there are no physiological measures which quantitate coronary blood flow categorizing obstructive to non-obstructive disease, these data are suggestive of the potential mechanisms by which miRs might be involved in plaque deposition and subsequent destabilization. While long theorized among miR evangelists, these data now establish a tangible potential therapeutic target for miRs toward these TCFAs in patients with established CAD.

Similar to our previous observations in patients with early coronary atherosclerosis and endothelial dysfunction, these authors note an increased transcoronary miR gradient in miR-126, miR-155, and miR-145 in patients with TCFAs. Interestingly, we reported these same findings in patients with very early CAD manifesting only by impaired coronary endothelial function. One of the potential weaknesses of this particular study—and most miR work to date—is its cross-sectional nature and its inability to harness temporal associations between the presence of miR or their fluctuations in transcoronary gradients. Nevertheless, piecing together previous work, it may allow the presumption that these miRs begin to appear in the coronary circulation in the early stages of CAD, and promote TCFA formation (Figure 1). Establishing a potential correlative timeline between coronary atherosclerosis and miR interaction could present potential therapeutic targets to seek out and arrest CAD. Another interesting and hypothesis-generating finding seen here is the notion of higher levels of arterial and venous miR-29 being associated with the destabilization of TCFAs, which could potentially lead to events driven by obstructive CAD. One could conceive that over time the transcoronary gradient of miR-29, and other miRs associated with matrix degradation such as miRs-100/101, could begin to increase (indicating net release into the coronary circulation) as plaques became unstable and more prone to rupture (Figure 1). The great unknown in this timeline is whether these increases in transcoronary gradients are a cause of atherosclerosis and TCFAs or whether these results are a byproduct of ongoing CAD progression. Our prior in vivo work would suggest the former, as miR-92a has been implicated in the initiation and progression of endothelial dysfunction, yet the current study appears only to implicate miR-92a in...
macrophage activity but not overall plaque or TCFA burden. These findings extend previous studies demonstrating the relationship between the presence of macrophages as detected by OCT and early coronary atherosclerosis. By combining vascular biology and imaging in small cohort studies performed at various time points in the continuum of CAD, this information could conceivably help construct a time course for targeting these specific miRs in the treatment of CAD throughout the disease course (Figure 1).

Unfortunately, very few human data exist regarding the continuum of miRs as they relate to CAD in humans. Previous work by our group has identified candidate miRs associated with coronary endothelial function, and others have identified candidate miRs elevated in patients with both acute and chronic CAD. The data presented here help fill in gaps in the timeline of the involvement of miRs in CAD, namely the potential involvement of certain miR candidates, miR-92, miR-126, miR-155, and miR-145, in the early phases of the development of coronary endothelial impairment ultimately leading to obstructive CAD. Subsequently, a new group of miRs, e.g., miR-29, could contribute to the destabilization and inflammation leading to obstructive CAD events. Thus, there are multiple potential therapeutic targets for patients at various stages of the progression of CAD, and techniques to stage an individual patient’s CAD coupled with delivery of specific miRs to these targeted areas should be further studied and delineated.

One of the major strengths of the current study is the unique intergraded method of transcoronary blood sampling and coronary imaging to investigate the mechanism of atherosclerosis in an ‘isolated’ artery in vivo in humans. Similar to previous studies in the field, the authors are burdened with the methodological difficulties faced in nearly every miR study in that there is no uniform method for quantitating and reporting results. These data inconsistencies across the field have led to conflicting reports of the potential roles of miRs in CAD, and will continue to restrict the implications of these findings toward larger therapeutic studies unless the reporting of relative miR quantifications can be standardized. This also begs the question regarding the specificity of miRs within the pathophysiological process of CAD. The fact is that most miRs target a multitude of factors and mechanistic pathways, hindering our ability to link them to a single pathophysiological cascade in the progression of CAD.

Another difficulty involves the methodological issues surrounding the miR research, in general, such as the lack of correction for multiple analyses with other variables and confounders. Work by De Rosa et al. incorporated a control group of seven patients with ‘normal’ coronary arteries; however, there is still an inherent selection bias as these patients had some clinical indication for being referred to the cardiac catheterization laboratory. Nevertheless, their important work not only introduced the notion of release/consumption of miRs via the measuring transcoronary gradients,
but also sheds some light on the coronary miR profile of patients without obstructive CAD.

The authors describe a standardization technique consisting of separate isolation of the tested miRs and the reference miRs (miR-574-5p and miR-3680-3p) that does differ slightly from their previous methods utilizing the ‘delta-CT’ method and Caenorhabditis elegans miR-39.6,12 These inconsistencies may not play a role in data discrepancies at this level, but have probably contributed to inconsistencies in different studies over time. One of the methods to overcome the inconsistencies within the field with regard to standardized quantification protocols used by different groups may include using the transcoronary gradient as in internal control. By measuring the gradient of endogenous factors potentially involved in the mechanism of coronary atherosclerosis in the same patients, one could potentially account for the contribution of systemic risk factors. Should the field ever move toward standardization and therapeutic use, laboratory and quantification standards will need to be initiated and upheld in human use.

The future and potential impact of miR research on CAD and plaque biology is limitless. Over the past 25 years not only have we identified this particular epigenetic contributor to CAD (among other such as non-coding RNAs—long and short, silencing RNA, and piwi RNA), but we are now probing how dozens of miRs could potentially be contributing to every aspect of CAD, from endothelial dysfunction to macrophage activation to plaque destabilization to fulminant acute coronary syndromes. Being able carefully to map which miR is associated with each pathophysiologic step in the CAD process could provide therapeutic tools to arrest and treat CAD. Given that many patients have different stages of CAD in their coronary arterial tree, therapeutic deliveries of miRs would probably need to be localized and tailored for each specific lesion. Furthermore, using epigenetics may very well help identify which particular patients may be more susceptible to CAD and its co-morbidities, or who may/not respond to optimal medical therapy to treat CAD. Indeed, we are yet to scratch the surface with regard to the contribution of the miR field to precision and individualized medicine as it relates to CAD.

Despite the methodological concerns that many in the field have, this particular work should be lauded for filling in an important gap in the timeline of miRs and CAD. The field should be sure to take note of these data, and attempt to coalesce around some commonalities lest another epigenetic phenomenon usurp the advances made by miR researchers and realize the full potential toward ameliorating CAD.

Conflict of interest: none declared.

References